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Assessment and Characterization of In Situ Rotator Cuff Biomechanics

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ASSESSMENT AND CHARACTERIZATION OF *IN SITU* ROTATOR CUFF
BIOMECHANICS

A Thesis
Presented to
the Graduate School of
Clemson University

In Partial Fulfillment
of the Requirements for the Degree
Masters of Science
Bioengineering

by
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May 2013

Accepted by:
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ABSTRACT

Rotator cuff disease is a degenerative disorder that is a common, costly, and often debilitating, ranging in severity from partial thickness tear, which may cause pain, to total rupture, leading to loss in function. In current clinical practice, treatment decisions are frequently made through subjective assessment of pain and range of motion combined with qualitative assessment of x-ray images, magnetic resonance images (MRI), or ultrasound images. Treatment of disease may include physical therapy, surgery, or a combination of both. Often, the final determination of the best course of action is at the discretion of the clinician, and is based on personal experience as opposed to quantitative standards.

Ultrasound is an inexpensive technique which can visualize and assess subsurface tissues in a reliable and noninvasive manner. Ultrasound acquisition techniques and image post-processing have been used for the non-invasive determination of tissue mechanical properties, in a process known as ultrasound elastography. Ultrasound elastography has shown much promise in the diagnosis of disease and disorder, though currently is largely used in specific anatomy such as breast.

The goal of this Master's thesis research was to develop a device to assess tissue biomechanics by quantitatively measuring the force applied to the underlying musculotendinous tissue while simultaneously obtaining the related ultrasound images. Once developed and calibrated, the device was validated using imaging phantoms with known elastic properties. A clinical evaluation of the device was performed to assess

device reliability *in situ* and to explore normal rotator cuff tissue biomechanics. These experiments included assessment of musculotendinous region of the infraspinatus, evaluating variability in tissue properties within a single patient and across a normal population.

The results presented in this thesis provide information regarding the *in situ* biomechanics of normal rotator cuff tendon. No significant difference in tissue properties was demonstrated within a single patient. This analysis demonstrated elastic moduli are variable across individuals and incidence. Therefore threshold elastic moduli will likely be a function of variation in local-tissue moduli as opposed to a specific global value. Further studies should explore the *in situ* biomechanics of both normal and diseased rotator cuff tendon to establish a narrowed range of normal elastic moduli and determine a range of threshold elastic moduli for the disease tissue type. Testing of diseased tissue at the various stages of disease progression will allow for an objective means to mark at risk tissues.

DEDICATIONS

This work is dedicated to my wonderful family. Their love, encouragement, and support in all of my endeavors has given me strength to pursue every goal and conquer every obstacle throughout my academic career. I would also like to recognize my late brother Logan, whose inquisitive mind and passion for engineering was a constant source of inspiration throughout my graduate work. I would not be where I am today without the support that each of you have given me through the years.

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CHAPTER ONE

INTRODUCTION

1.1 Rotator Cuff Anatomy and Physiology

The rotator cuff is composed of four muscles, these are the supraspinatus, infraspinatus, teres minor, and subscapularis (Figure 1). These muscles end in short, flat, broad tendons which fuse with the fibrous capsule to form the musculotendinous cuff (Figure 2) [1,2].

Figure 1. Anterior and posterior view of healthy rotator cuff anatomy.

Figure 2. Cover insert that the tendons of the rotator cuff form around the humeral head.

The four muscles and tendons of the rotator cuff act as the dynamic stabilizer of the glenohumeral joint and each play an important role in the motion of the shoulder (Figure 3). The main function of the supraspinatus tendon is the initiation abduction with the assistance of the deltoid; additionally, this tendon initiates the first 30 degrees of forward flexion and has a role in the external rotation of the humerus. The primary role of both the infraspinatus and teres minor is in the external rotation of the humerus. The subscapularis tendon functions as the main internal rotator of the humeral head in relation to the scapula. Composition and structure of each tendon in the rotator cuff differ when compared to one another but are primarily composed of Type I and Type III collagen. In healthy rotator cuff tissue, Type I collagen predominates; however, with degeneration, age, and tearing of rotator cuff tissue the amount of Type III collagen increases [3].

Figure 3. Motions of the shoulder controlled by the rotator cuff muscles and tendons. (Left) Initiation abduction. (Center) External rotation of the humerus. (Right) Internal rotation of the humeral head.

1.2 Rotator Cuff Pathology and Disease Classification

The pathological progression from healthy to diseased tendon is not fully explained. Mechanisms of tendinopathy have been classically described as extrinsic, intrinsic, or a combination of both. Extrinsic factors are broadly grouped into traumatic and anatomical factors such as hooked, curved, and laterally sloping acromions, which are strongly associated with cuff tears [4]. Other anatomical extrinsic factors include coracoacromial arch narrowing or mechanical impingement, during which cuff fibers are compressed by soft tissue and bone [3,4]. Intrinsic factors encompass a range of mechanisms that occur within the rotator cuff itself due to the natural process of aging, poor vascularity, altered biology, and inferior mechanical properties; chief among these mechanisms is a degenerative-microtrauma model [2,3]. In many patients, it is likely their pathologic abnormality is a byproduct of the interaction between both intrinsic and extrinsic factors.

Rotator cuff tears are traditionally classified according to their depth (Figure 4). Full thickness tears or ruptures extend from the articular surface to the bursal surface of the tendon. Partial thickness or incomplete tears involve only the articular surface or the bursal surface of the tendon and an intrasubstance or intratendinous tear is a tear within the substance of the rotator cuff and does not extend [2,5].

Figure 4. Rotator cuff tear classification. (*Left*) Full thickness tear or rupture extending from the articular surface to the bursal surface of the tendon. (*Center*) Partial thickness tear on the articular surface of the tendon. (*Right*) Partial thickness tear on the bursal surface of the tendon.

1.3 Current Rotator Cuff Disease Treatments

Patients with possible rotator cuff tears commonly present with complaints of shoulder pain, stiffness, weakness, or loss of motion. Currently, clinical diagnosis and determination of disease extent is based primarily on the results of patient history, subjective assessment of pain, range of motion, and x-ray, magnetic resonance (MRI) or

ultrasound images [6]. Clinicians then use the collected information to classify and stage the disease, providing diagnosis and treatment recommendations as well as determining long-term prognosis. Detection and early treatment are critical; if left untreated rotator cuff disease can result in significant loss of shoulder function and range of motion. Therefore, recognizing the specific site of occurrence, size, and extent of the rotator cuff injury are important factors for determining the best outcome for the patient [7]. There is, however, little objective data upon which to base detection and staging, often resulting in costly and unpredictable patient outcomes.

Treatment of disease may include physical therapy, surgery, or a combination of both however there is no simple treatment algorithm for partial-thickness rotator cuff tears. Nonsurgical treatment is the typical plan of care for patients with partial thickness tears who are not experiencing severe pain or significant weakness. This includes the use of non-steroidal anti-inflammatory drugs, intermittent steroid injections, activities modification, and physical therapy [8,9]. Nonsurgical treatment does not lead to healing of the rotator cuff but the remaining intact portion of the tendon may compensate for the torn portion, which may lessen symptoms. Surgical intervention is considered for those patients who have failed 3 to 6 months of conservative nonsurgical treatment as well as those patients with full thickness tears [8,9]. A surgical recommendation should consider patient specific factors such as the magnitude of the current symptoms, level of physical activity, and size of rotator cuff tear. Although surgical intervention and conservative rehabilitation are effective treatments for many patients, it is unclear which patients are

most likely to benefit from each treatment option resulting in high failure rates of rotator cuff repairs [10].

1.4 Current Imaging Technology for the Assessment of Rotator Cuff Disease

There are several imaging modalities aimed at improving the staging of rotator cuff disease these include x-ray, MRI, and ultrasound however, each modality has drawbacks in the detection of rotator cuff tears. Plane-film radiographs are an important component of evaluating a patient with shoulder pain and frequently reveal bone abnormalities such as subacromial spurs which provides information in regards to the condition of the rotator cuff (Figure 5) [11]. However, radiographs are rarely helpful in making the diagnosis of a partial-thickness rotator cuff tears.

Figure 5. Anteroposterior radiograph of a rotator cuff with a subacromial spur. The arrow indicated the location of the subacromial spur.

Magnetic resonance imaging (MRI) can reveal a high degree of specificity in the detection of rotator-cuff tears (Figure 6). Often a combination of T1-weighted and T2-weighted images are used in the analysis of the rotator cuff and are performed using the transverse, coronal oblique, and sagittal oblique imaging planes [11]. MR arthrography can demonstrate an even higher degree of accuracy in the assessment of the rotator cuff injuries and is helpful in the detection of partial-thickness tears, which become more conspicuous following intra-articular contrast injection [7,9,11]. Although MRI and MR arthrography demonstrate high accuracy, they are costly and intra-articular contrast injections are invasive. Further, standard MRI imaging provides no dynamic, real time data on which to base clinical decisions.

Figure 6. Magnetic resonance image of a partial thickness rotator cuff tear. The arrows indicate the location of the rotator cuff tear.

As opposed to plane-film x-ray and MRI, ultrasonography is a dynamic, reliable, noninvasive, widely available, and inexpensive technique. Ultrasound can be used for assessing soft tissue involvement in musculoskeletal disease [11-14]. Various rotator cuff diseases can be effectively evaluated and diagnosed using ultrasonography (Figure 7). To ensure a comprehensive and efficient examination of the shoulder using ultrasound, a scanning protocol should be followed such that key structures are examined (Table 1) [13]. Despite the use of scanning protocols, accurate results are operator dependent and images often lack specific anatomic context, limiting their clinical utility, especially for long term evaluation of treatment effectiveness or disease progress [13].

Figure 7. Longitudinal sonographic assessment of the rotator cuff. Anatomical features are indicated. (D) Deltoid muscle (RC) Rotator cuff (c) Cartilage of the humeral head (H) Humeral head.

Table 1. Ultrasound protocol used for the examination of the shoulder and rotator cuff.

<i>Step Number</i>	<i>Protocol</i>
1	Biceps brachii tendon, long head
2	Subscapularis and biceps brachii tendon, subluxation/dislocation
3	Supraspinatus and rotator interval
4	Acromioclavicular joint subacromial-subdeltoid bursa, and dynamic evaluation for subacromial impingement
5	Infraspinatus, teres minor, and posterior labrum

1.5 Ultrasound Elastography

Ultrasound imaging allows for the noninvasive, *in situ* assessment of tissue mechanical properties through a method called ultrasound elastography (UE) [15-18]. It is believed that diseased or injured tissue will behave differently under compression than healthy tissue, exhibiting aberrant biomechanical properties such as stiffness and failure load. When performing ultrasound elastography the ultrasound probe is used to exert pressure on the tissue being examined resulting in compression (Figure 8). Ultrasound images are obtained before and during tissue compression or extension from which tissue strain can be calculated. By measuring the amount of tissue displacement and either the acquired signals or applied force before and after tissue displacement, objective information regarding tissue stiffness can be obtained (Figure 8) [16,17]. Ultrasound elastography has been successfully employed in the assessment of the various normal and abnormal tissues including those in the breast, prostate, thyroid, cervix, lymph nodes, pancreas, and liver. Few studies however have investigated the use of ultrasound elastography in the characterization of musculoskeletal biomechanics.

Figure 8. Diagram of the methodology of ultrasound elastography. (a) The ultrasound transducer is used to exert a force on the underlying tissue resulting in compression of the tissue. (b) Resulting tissue displacement is measured. This information coupled together provides analysis of tissue strain.

There are three main types of elastographic techniques including freehand elastography, transient elastography, and acoustic radiation force impulse (ARFI). Real time freehand ultrasound elastography is the simplest technique, which uses a gentle freehand compression to apply stress to the underlying tissue resulting in a displacement in the longitudinal direction. The resulting strain is displayed as a color overlay on a conventional B-mode ultrasound image (Figure 9) [17-19]. Free hand elastography has been shown to be helpful in breast and prostate tumor detection, thyroid tumor diagnosis, intravascular plaque characterization, and assessment of tendinosis [16]. There are however limitations to free hand ultrasound elastography such as operator dependence, reproducibility, and qualitative rather than quantitative assessment [19].

Figure 9. Diagram of the method of freehand ultrasound elastography. The ultrasound transducer is used to manually compress the underlying tissue resulting in a measurable strain.

Transient elastography transmits a shear wave into the underlying tissue, which is soon followed by the transmission of an ultrasound wave (Figure 10) [20]. Using Doppler technique, the velocity of the mechanical shear wave in the tissue is calculated. Increases in wave velocity are related to the stiffness of the underlying tissue. This method of elastography avoids a bias related to reflected waves created at tissue boundaries which is a drawback in other methods. Transient ultrasound elastography is mainly used in examination of liver disease, though other applications include breast tumor detection and muscle stiffness measurement [16,18].

Figure 10. Schematic of transient ultrasound elastography technique. A shear is transmitted into the underlying tissue, which is soon followed by the transmission of an ultrasound wave. Doppler technique is used to measure the velocity of the mechanical shear wave in the tissue.

In contrast to the above described methods, ARFI imaging uses internal tissue excitation through focused short-duration acoustic radiation forces to generate localized displacements in tissue, which are then tracked using ultrasonic correlation-based methods [21]. The response of the underlying tissue to these forces can be monitored both spatially and temporally and the magnitude of local tissue displacement is inversely proportional to tissue stiffness (Figure 11). Acoustic radiation force elastography has been applied to breast lesion imaging, abdominal imaging, as well as providing guidance for cardiac and liver tissue ablation [16].

Figure 11. Schematic of Acoustic Radiation Force Elastography (ARFI). Short-duration acoustic radiation forces are used to generate localized displacements in the underlying tissue and are tracked using ultrasonic correlation-based methods.

1.6 Commercially Available Ultrasound Elastography Systems

Currently several commercial ultrasound systems offer quasi-static based strain imaging modes on their clinical systems. These systems are produced by a number of vendors each are designed with a specific diagnostic function or range of elastographic functions.

The Siemens ACUSON series employs acoustic radiation force elastography or freehand compression elastography depending on the software technology. The clinical utility of this system is aimed toward detection of liver fibrosis and lesions. The Hitachi real-time tissue elastography system by Hitachi medical systems uses freehand compression in conventional B-mode ultrasound. The system has proven diagnostic value in a variety of clinical areas most notable breast, urology, pancreas, and lymph nodes and

has also shown promise in musculoskeletal applications. The SonixTOUCH by Ultrasonix Medical Corporation uses freehand compression elastography. Echosens has several elastography systems that are currently available. The most notable is the FibroScan system, which uses transient elastography for detection of liver fibrosis. Philips' iU22 systems uses freehand compression and has shown significant clinical utility in breast lesion detection. Lastly, General Electric offers the Logiq e9 which also uses freehand compression elastography and has clinical utility in a variety of areas.

The discussed commercially available ultrasound elastography systems provide qualitative information regarding tissue stiffness based on relative differences in tissue movement. Strain data is frequently converted into color scale images and superimposed on to the B-mode images to facilitate their use in clinical practice. Color mapping varies depending on the system for example, Philips ultrasound elastography systems depict malignant lesions in blue whereas benign lesions appear in red. In contrast, Siemens free hand elastography system displays malignant lesions in red whereas benign lesions are blue. It is possible to derive semi-quantitative strain indices on the elasticity maps obtained by comparing the strain levels of different normal appearing areas of the breast with the strain level of the lesion [22]. While the different elastography modes and color mapping have been shown in various studies to help in the differentiation between benign and malignant breast and liver lesions, achieving consistency in the application of the technique and developing optimized protocols dedicated to musculoskeletal applications are of paramount importance to the clinical utility of ultrasound elastography as a diagnostic tool for musculoskeletal disorders [23, 24]. Furthermore, the algorithms which

obtain completely quantitative strain data to support the qualitative color mapping currently used would greatly enhance the clinical utility of ultrasound elastography [23].

CHAPTER TWO

DEVICE DEVELOPMENT AND PHANTOM VALIDATION

2.1 Abstract

Rotator cuff disease is a most common cause of shoulder pain and dysfunction in adults, ranging in severity from partial thickness tear, which may cause pain, to total rupture, leading to loss in function. Currently, determination of disease extent relies primarily on patient history, subjective assessment of pain, range of motion tests, and imaging studies. The final treatment plan however is at the discretion of the clinician, who often base their decision on personal experiences, and not quantitative standards.

The use of ultrasound for the assessment of tissue biomechanics is established, such as in ultrasound elastography, where soft tissue biomechanics, typically in the breast, are measured. Few studies have investigated the use of ultrasound elastography in the characterization of musculoskeletal biomechanics. To assess tissue biomechanics we have developed a device, which measures the force applied to the underlying musculotendinous tissue while simultaneously obtaining the related ultrasound images. In this study we aim to validate and obtain preliminary measurements using this device.

2.2 Introduction

Rotator cuff disease affects more than half the population over 60, leading to pain or debilitation, causing a significant burden on the healthcare system [25,26]. Approximately half of those with this degenerative condition will deteriorate to the point of total cuff rupture, requiring surgical repair [27]. Early detection and intervention,

including physical therapy, surgical treatment, or both, has been shown to improve the outcome of patients with rotator cuff disease; however, from a biomechanical perspective, the critical stage at which surgical intervention is recommended remains unknown [28]. The lack of diagnostic tools capable of providing quantitative assessment requires clinicians to make subjective decisions on the best course of treatment. Consequently, there is a lack of standardized diagnosis across physicians and thus inconsistent or incorrect staging of rotator cuff disease that can lead to unnecessary, inappropriate, and expensive treatments that may or may not benefit the patient. In many cases, MRI imaging is used for the differential diagnosis and measurement of disease extent. However, MRI is expensive, time consuming, and does not provide real time motion. Furthermore, MRI provides a limited analysis of the disease state at high cost, making MRI frequently impractical.

In contrast, ultrasound is inexpensive making it practical for use in a doctor's office or physical therapy clinic. A recent study demonstrated that a change by as little as 1% from MRI to ultrasound imaging correlates to a cost savings to Medicare and Medicaid of approximately \$1 million [29]. Further, ultrasound allows for real-time image acquisition producing dynamic images allowing for assessment of both anatomy and function. There is no risk to the patient from ultrasound, as there is no use of ionizing radiation, allowing for repeated examination over time to monitor patient progress. Ultrasound imaging allows for the measurement of *in situ* tissue stiffness through a method called ultrasound elastography (UE) [14,15,30]. In UE the ultrasound probe is used to exert pressure on the tissue being examined resulting in compression (Figure 12).

Processing of the images allows for computation of the mechanical properties of the tissues under test.

Figure 12. Typical ultrasound images of musculetendinous tissue, under (*left*) no compression and (*right*) moderate compression. The tissue boundaries are visible, and thus the change in the tissue thickness due to compression can be computed.

The purpose of this study is to validate the developed force-measuring device, utilizing it to evaluate materials of known elastic modulus.

2.3 Materials and Methods

The elasticity of a material is defined by a quantity known as Young's Modulus (E), which is a function of stress (σ) and strain (ϵ). Stress is a property of an applied force

(F) applied over a surface area (A), while strain is a change in the length of a material (ℓ) as a function of its original length (ℓ_o). This relationship is shown in Eqn. 1, in which local elasticity in tissues can be computed given a known transducer size (area) and the measurement of the applied force at the ultrasound transducer. The length and change in length can be measured from the resulting ultrasound images.

$$\sigma = \frac{F}{A} \quad \varepsilon = \frac{\Delta \ell}{\ell_o} = \frac{\ell - \ell_o}{\ell_o} \quad E = \frac{\sigma}{\varepsilon} = \frac{(F/A)}{(\ell - \ell_o/\ell_o)} = \frac{F(\ell_o)}{A(\ell - \ell_o)} \quad \text{Eqn. 1}$$

2.3.1 Device Development

The developed force measuring device is composed of an open body frame with upper and lower members derived from cut acrylic (Figure 13). The upper and lower members of the body frame are spaced in an adjustable manner using two rods each surrounded by a coil spring. The adjustability of the spacing allows for various existing ultrasound probe models to be contained within the center of the device. The lower member of the body frame is open which allows for the distal end of the ultrasound probe to extend, in order to make contact with the skin of the patient and assess the underlying tissue. Two flex sensors are aligned parallel and adjacent to the coil springs. When the device is placed in contact with the skin, the lower member translates toward the upper member, compressing the coil springs toward the upper member and flexing the sensors outward in response to the inward compression of the target tissue by the ultrasound probe. Using a Wheatstone bridge circuit for each of the flex sensors, the change in resistance is converted into voltage changes. These voltage changes are captured, averaged and displayed by an Arduino Uno microcontroller.

Figure 13. Developed force measuring device. (*Left*) Device and housed circuit without an ultrasound probe contained within the center of the device. (*Right*) Device with an ultrasound probe contained within the center of the device.

To calibrate the developed force measuring device, hooked weights were hung from the center of the device in manner that caused an even compression. For each weight the corresponding voltage change was recorded. This was repeated in 0.5 kilogram increments beginning at 0.8 kilograms and continuing to 1.3 kilograms. Four trials were conducted. The voltages were averaged and a linear regression was plotted to determine a calibration curve for the force measured by the device (Figure 14).

Figure 14. Flex sensor calibration curve. The calibration curve was determined to be monotonic linear ($R^2 > 0.99$). The calibration curve was used to convert the recorded voltages to force values.

2.3.2 Phantom Validation

Three polyvinyl alcohol cryogel (PVA-C) phantoms of the same formulation were created and analyzed using our elastography system in order to determine the ability of the developed force measuring device accurately assess material stiffness. During the validation study, the material was subjected to stress using our ultrasound transducer, and strain was assessed from the ultrasound images using a manual measurement (Figure 15). This method was repeated ten times for each phantom.

Figure 15. Ultrasound images of the PVA-C phantoms. (*Left*) PVA-C phantom in a non-compressed state. (*Right*) PVA-C phantom under compression due to applied stress of ultrasound transducer.

A second phantom made of Ecoflex30, a platinum-catalyzed silicon, produced by Smooth-On Inc. (Easton PA), was analyzed using our elastography system in the same manner as in the previous PVA-C study. Compression tests of the Ecoflex30 were conducted using a Bose ElectroForce 3200 to determine the Young's modulus of the material.

2.4 Results

The stress and strain values for the ten trials were averaged. This was done for each of the three PVA-C phantoms. Using the averaged values, the stress-strain curves were plotted and were found to be monotonic linear ($R^2 > 0.98$). The determined Young's modulus for all three of the PVA-C phantoms fit within the range of 20-42.8 kPa is shown in the literature for this formulation (Figures 16-18).

Figure 16. Measured stress-strain curve of the first polyvinyl alcohol crygel (PVA-C) phantom. Monotonic linear ($R^2 > 0.99$), with an inherent dampening offset of 2.4996 kPa and a Young's modulus of 30.291 kPa.

Figure 17. Measured stress-strain curve of the second polyvinyl alcohol crygel (PVA-C) phantom. Monotonic linear ($R^2 > 0.98$), with an inherent dampening offset of 2.5315 kPa and a Young's modulus of 34.385 kPa.

Figure 18. Measured stress-strain curve of the third polyvinyl alcohol cryogel (PVA-C) phantom. Monotonic linear ($R^2 > 0.98$), with an inherent dampening offset of 2.2145 kPa and a Young's modulus of 35.079 kPa.

The Young's modulus of Ecoflex30 was determine to be 53.02 kPa at approximately a 10 percent strain using the Bose ElectroForce 3200. Air bubbles cast within Ecoflex30 caused attenuation of the ultrasound signal resulting in an inaccurate ultrasound image and thus an invalid measurement of the material deformation (Figure 19). To eliminate the signal attenuation, the deformation of the Ecoflex was measured by hand using a standard ruler and the Young's modulus was determined to be 57.39 kPa at approximately a 9 percent strain.

Figure 19. Ultrasound image of Ecoflex30. The arrow indicates the bubbles increasing the attenuation of the ultrasound signal.

2.5 Discussion

Previous studies have shown that PVA-C phantoms have low acoustic attenuation, and the impedance and speed of sound that are similar to biological tissue because they mainly consist of water. These properties allow for the strain to be accurately determined from the resulting ultrasound images. Additionally, numerous studies have evaluated the elastic properties for the PVA-C formulation used in this study. When subjected to testing with the developed device, material stiffness was accurately assessed using the obtain ultrasound strain information and force data.

Silicone polymers, such as the Ecoflex30 phantom used in this study have a significantly lower speed of sound and higher acoustical attenuation than water and human tissue. In addition to these material properties, bubbles cast within the phantom during fabrication further increased the acoustic attenuation during ultrasound examination of the phantom. The properties of silicone polymers in combination with the bubbles prevented accurate measurement of strain from the resulting ultrasound images. When the deformation of the Ecoflex phantom was measured by hand using a standard ruler, the determined Young's modulus was found to be similar to the Young's modulus determined during the Bose ElectroForce testing. Due to its lower speed of sound, the silicone phantom was found to be less suitable for device validation than the PVA-C phantom.

Although signal attenuation was problematic when determining material stiffness for the Ecoflex phantom using ultrasound, it is unlikely that signal attenuation will affect the accuracy of the device *in situ*. The developed force measuring device correctly determined the stiffness of PVA-C phantoms which have properties that are similar to those found in biological tissues, suggesting that in future *in situ* studies the device will accurately determine tissue stiffness.

The *in vitro* validation studies demonstrate the ability of the developed force measuring device to accurately assess material stiffness from the measured force and ultrasound strain information. Therefore, based on preliminary data we expect to accurately compute tissue stiffness *in situ*.

2.6 Conclusions

We believe that by utilizing ultrasound elastography it will be possible to assess the risk for and the extent of rotator cuff disease, allowing for early diagnosis and appropriate treatment. Subsequent testing of diseased tissue at various stages of disease progression will allow for the determination of a threshold value of the various stages of rotator cuff disease allowing an objective mean to mark tissues at risk. Furthermore, validation of ultrasound as a reliable and accurate means by which to stage this disease would significantly decrease the societal cost associated with rotator cuff disease. Therefore, through this early diagnosis, we believe there can be a net reduction in the necessary treatment, and thus total cost of this common and debilitating condition.

CHAPTER THREE

ASSESSMENT OF *IN SITU* ROTATOR CUFF BIOMECHANICS IN A HEALTHY POPULATION

Portions of this chapter were published in:

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3. 1 Abstract

Rotator cuff disease is a degenerative disorder that is a common, costly, and often debilitating, ranging in severity from partial thickness tear, which may cause pain, to total rupture, leading to loss in function. Currently, clinical diagnosis and determination of disease extent relies primarily on subjective assessment of pain, range of motion, and possibly X-ray or ultrasound images. The final treatment plan however is at the discretion of the clinician, who often bases their decision on personal experiences, and not quantitative standards.

The use of ultrasound for the assessment of tissue biomechanics is established, such as in ultrasound elastography, where soft tissue biomechanics are measured. Few studies have investigated the use of ultrasound elastography in the characterization of musculoskeletal biomechanics. To assess tissue biomechanics we have developed a device, which measures the force applied to the underlying musculotendinous tissue while simultaneously obtaining the related ultrasound images. In this work, the

musculotendinous region of the infraspinatus of twenty asymptomatic male organized baseball players was examined to assess the variability in tissue properties within a single patient and across a normal population. Elastic moduli at percent strains less than 15 were significantly different than those above 15 percent strain within the normal population. No significant difference in tissue properties was demonstrated within a single patient. This analysis demonstrated elastic moduli are variable across individuals and incidence. Therefore threshold elastic moduli will likely be a function of variation in local-tissue moduli as opposed to a specific global value.

Keywords: Ultrasound elastography, tissue biomechanics, rotator cuff, musculoskeletal, quantitative

3.2 Introduction

Rotator cuff disease is a common and costly condition, affecting more than 50% of the population age 60 and over [6]. Current belief is that rotator cuff disease is a degenerative condition, worsening with time. Clinical severity can range from partial to full thickness tendon tears. The impact of rotator cuff disease on a patient's quality of life, function, and comfort is comparable to that of congestive heart failure, diabetes, myocardial infarction, and depression as determined by numerous studies using the SF-36 health survey [31]. Early detection and intervention, including physical therapy, surgical treatment, or both, has been shown to improve the outcome of patients with this disease;

however, from a biomechanical perspective, the critical stage of rotator cuff tear at which surgical intervention is recommended remains unknown [28].

Currently, clinical diagnosis and determination of disease extent is based primarily on the results of patient history, subjective assessment of pain, range of motion, and X-ray or ultrasound images [13]. Clinicians then use this information to classify and stage the disease to provide diagnosis and treatment recommendations as well as determine long-term prognosis. Detection and early treatment are critical; if left untreated rotator cuff disease can result in significant loss of shoulder function and range of motion. Therefore, recognizing the specific site of occurrence, size, and extent of the rotator cuff injury are important factors for determining the best outcome for the patient [7]. There is, however, little objective data upon which to base detection and staging, often resulting costly and unpredictable patient outcomes.

The lack of diagnostic tools capable of providing quantitative assessment requires clinicians to make subjective decisions on the best course of treatment. Consequently, there is a lack of standardized diagnosis across physicians and thus inconsistent or incorrect staging of rotator cuff disease that can lead to unnecessary, inappropriate, and expensive treatments that may or may not benefit the patient. Available imaging technology aimed at improving the staging of rotator cuff disease may provide immediate clinical benefit; however, each modality has drawbacks. In many cases, MRI imaging is used for the differential diagnosis and measurement of disease extent. MRI is expensive, time consuming, and does not provide real time motion. MRI provides a limited analysis of the disease state at high cost, making MRI frequently impractical. In contrast to MRI,

ultrasonography is a dynamic, reliable, noninvasive, widely available, and inexpensive technique for assessing soft tissue involvement in musculoskeletal disease [32]. Various rotator cuff diseases can be effectively evaluated and diagnosed using ultrasonography; however, accurate results are operator dependent and images often lack specific anatomic context, limiting their clinical utility [13].

Ultrasound imaging allows for the noninvasive, *in situ* assessment of tissue mechanical properties through a method called ultrasound elastography (UE) [14]. While initial clinical applications of UE have been largely in tumor detection, its usefulness has recently increased in the musculoskeletal field [33]. In UE the ultrasound probe is used to exert pressure on the tissue being examined resulting in compression, producing a strain within the tissue. When performing ultrasound elastography, images are obtained before and during tissue compression from which tissue strain can be calculated. By measuring the amount of tissue displacement and the applied force before and after tissue displacement, objective information regarding tissue stiffness can be obtained [14,15,30].

Classically, the clinical application of ultrasound elastography provides a qualitative measure of tissue stiffness [19]. In musculoskeletal applications the lack quantitative assessment requires clinicians to make subjective assessment of disease extent. Objective quantification of tissue stiffness would provide a useful tool for the characterization of tendon health and lead to standardization of diagnosis across physicians. Therefore, the purpose of this study is to further validate the developed force-measuring device in the quantification of the *in situ* tissue elastic moduli, utilizing it to evaluate the infraspinatus of twenty healthy volunteers.

3.3 Materials and Methods

3.3.1 Study Population

The musculotendinous region of the infraspinatus of twenty male subjects (mean age 20 years; range 15-25 years) was examined. All subjects were asymptomatic organized baseball players. No subjects had any history of pain within the past three months, a history of tendon injury, or history of surgery on either shoulder. The institutional review board approved this study, and informed consent was obtained from all volunteers.

3.3.2 Examination Protocol

The examination of all volunteers included B-mode scanning using the same commercially available ultrasound system (M-Turbo, SonoSite, Inc., Bothell, WA) and the same transducer (HFL50x 15-6MHz) fitted with the developed force-measuring device. All evaluations were performed by a physical therapist with significant experience using ultrasound to image and evaluate shoulder pathology. The volunteer was examined in the sitting position. The transducer was placed within the long axis of the infraspinatus muscle at the level of the posterior glenohumeral joint line, inferior to the spine of the scapula (Figure 20). Each ultrasound image was centered along the spinoglenoid notch, and standardized measurements were calculated (Figure 21).

Figure 20. Patient set-up for dynamic ultrasonography of the musculotendinous region of the infraspinatus.

Figure 21. Static ultrasonographical view of the infraspinatus and the spinoglenoid notch landmark.

During ultrasound examination, manual compression was applied to the underlying tissue using a freehand technique and images were stored as cineloops. Recording began with the tissue under no compression and continued until a maximal compression of the underlying tissue was reached (Figure 22). Correlating force data from the force-measuring device was recorded for the points of no compression and maximal tissue compression. Video of two separate compressions was obtained on the same day for a given volunteer. Volunteers were evaluated on two separate instances. In total four measurements for each tendon were made.

Figure 22. Ultrasound images of the musculotendinous region of the infrapinatus. (A) Infrapinatus under no compression. (B) Infrapinatus under maximal compression.

3.3.3 Data Analysis

The acquired ultrasound images were evaluated using a manually applied region of interest to segment tissue boundaries and determine local strain. The elastic modulus

was computed using the calculated local strain and correlating applied force data. Video files from each study were encoded to maintain volunteer anonymity.

3.4 Statistical Analysis

For further analysis of the collected data, measured stress and elastic moduli were grouped based on the induced percent strain of the infraspinatus to account for the viscoelastic properties of musculotendinous tissue. The data from the individual trials was divided into three strain groups set at 5 percent increments: 10-15% strain, 15-20% strain and 20-25% strain. Strain data that was above or below the three strain groups was eliminated for this portion of the analysis. The division of the data included 86.3 percent of all data. For all analyses, p-values <0.05 were considered significant. Statistical analysis was performed using Minitab 16 Statistical Software (State College, PA, USA). The variance of the measured stress within strain groups was analyzed using a Levene's test and One-Way Analysis of Variance (ANOVA). Variance of the elastic moduli for an individual and for the normal population were analyzed using One-Way ANOVA and Fisher tests.

3.5 Results

In assessing the tissue biomechanics, we first examined the measured stress values within the three strain groups to assess the reliability and function the device *in vivo* (Table 2). No significant difference in terms of variance of the measured stress was demonstrated between the strain groups when compared (Table 3).

Table 2. Population description for the Strain groups. N represents the number of measurements contained within the percent strain interval.

Strain Group	N	Mean Stress	Standard Deviation	Variance
10-15%	26	14.8	4.28	18.3
15-20%	33	14.9	4.44	19.7
20-25%	10	16.7	4.51	20.3

Table 3. Population statistics for strain groups using Levene's Tests.

Strain Group Comparison	p-value
10-15% and 15-20%	0.963
15-20% and 20-25%	0.760
10-15% and 20-25%	0.789

Examining of the determined elastic moduli of the infraspinatus within the normal population demonstrated that elastic moduli at percent strains less than 15 were significantly different than those above 15 percent strain within the normal population ($p=0.001$). There was no significant difference demonstrated in elastic moduli for strain groups above 15 percent.

In looking at the elastic moduli determined for individual volunteers, the data from the first examination compared to the second examination demonstrated no significant difference ($p>0.05$). The histogramical representation of the elastic moduli for the study population demonstrated a moderately symmetric, unimodal distribution with a major peak at 85-95 kPa (Figure 23). The mean elastic modulus of the normal population was determined as 96.1 kPa.

Figure 23. Histogram of the elastic moduli determine in the infraspinatus study.

3.6 Discussion

In evaluating the reliability and variance of the developed force-measuring device *in situ*, it was determined as in previous PVA-C phantom studies that the device quantitatively measures the stress applied to the underlying tissue in a consistent and reproducible manner while simultaneously obtaining the correlating ultrasound images.

The mean elastic modulus of 96.1 kPa was larger than elastic moduli values reported in the literature for the muscle, ranging from 1.8-57 kPa [17]. The musculotendinous junction of the infraspinatus exhibits mechanical properties of both

muscle and tendon due to the integration of both tissue types at this location. Therefore the combination of mechanical properties is likely the reason for the larger than expected elastic modulus.

The significant difference between elastic moduli below 15 percent and above 15 percent is likely due to the viscoelastic nature of the musculotendinous tissue as well as possible difference in the loading of the stress on the underlying tissue. No significant difference was found for the elastic moduli for a given individual, however the histographical representation of the observed elastic moduli suggests that elastic moduli are variable across individuals and incidence. Therefore threshold values for both healthy and diseased tissue will likely be a function of variation in local-tissue modulus as opposed to a specific global value.

This study has a number of limitations. First the study population (20 asymptomatic organized baseball players) was relatively small. Additionally, due the athleticism of the study population the elastic modulus values may not adequately depict the values that occur in the normal population. Second, in terms of ultrasound elastography the application of pressure to the probe to the underlying tissue has a relatively high operator dependency. Pressure applied to the probe to reach maximal compression was subjective and based on when the operator could no longer compress the underlying tissue with the ultrasound probe. Therefore the amount of pressure was not necessarily consistent in between trials for a given patient. In further studies, ensuring that the same pressure is applied or the same compression is reach during each trial

instead subjectively applying pressure until maximal compression is reached would increase the significance of the study.

3.7 Conclusions

Utilizing ultrasound elastography in musculoskeletal applications such as assessing the risk for and determining the extent of rotator cuff disease would allow for early diagnosis and standardization of treatment. In this work we have demonstrated the reliability and consistency of our force-measuring device for the application of quantitative ultrasound elastography. Continued testing of healthy tissue will allow for a narrowed range of normal elastic moduli, aiding in the establishment of a threshold value for normal tissue. Subsequent testing of diseased tissue at various stages of disease progression will allow for the determination of a threshold value of the various stages of rotator cuff disease allowing an objective mean to mark tissues at risk. Our preliminary findings suggest that our ultrasound elastography system can be used as a reliable and accurate means to access *in situ* tissue biomechanics. Utilizing ultrasound elastography to stage rotator cuff disease would significantly decrease the societal cost associated with this disease resulting in a net reduction in the necessary treatment, and thus total cost of this common and debilitating condition.

CHAPTER FOUR

CONCLUSIONS

Rotator cuff disease is one of the most common causes of shoulder pain and disability and is becoming increasingly prevalent with the growing elderly population. Currently there is no definitive algorithm used for the determination of disease extent or necessary course of treatment. Furthermore, many of the guidelines used to determine the course of treatment are arbitrarily chosen based on limited clinical evidence. Effective evidence-based treatments using quantitative standards are of a high priority as occurrence and treatment cost continue to rise. Ultrasound elastography has shown much promise in the diagnosis of disease and disorder in the breast, thyroid, prostate and lymph nodes however few studies have investigated the use of ultrasound elastography in the characterization of musculoskeletal disorders.

This research has many implications for a potential diagnostic tool for musculoskeletal pathologies. The developed force measuring device has demonstrated reliability and consistency for the application of quantitative ultrasound elastography in both *ex vivo* phantom analysis and *in vivo* musculotendinous analysis. The novel assessment of musculotendinous tissue using ultrasound elastography allows for determination of baseline tissue properties using *in situ* techniques. This *in situ* assessment differs from currently established values, which largely come from cadaveric specimens.

Using the developed device for quantitative ultrasound elastography shows promise for the diagnosis and staging rotator cuff disease progression, allowing standards-based planning for appropriate intervention. A quantitative method to measure and mark musculotendinous tissues in question would significantly decrease the economic and societal costs associated with rotator cuff disease, ideally resulting in a net reduction in the necessary treatment. Through this method a total reduction in the costs associated with this common and debilitating condition is possible.

CHAPTER FIVE

RECOMMEDATIONS FOR FUTURE RESEARCH

1. Development of software prototype for the semi-automatic segmentation of a region of interest and production of a color overlay onto the collected ultrasound images.
 - a. A semi-automation approach will more accurately detect the region of interest. This approach will require less user interaction than the fully manual approach. The color overlay will show both visually and quantitatively the associated elastic modulus values.
2. Fabrication of a layered testing phantom of varying elastic moduli similar to layers of natural tissues present in human shoulders.
 - a. Development of this type of phantom will enhance device calibration. A layered phantom will also provide an accurate means for *ex vivo* device and software validation.
3. Comparative study of the developed protocol versus current standard of care.
 - a. This type of study will evaluate the accuracy of clinical diagnosis using our system. The clinical utility our system presents will be determined in relation to the current standard of care.
4. Formation of a database of material properties based on the testing of normal and diseased rotator cuff tendons.

- a. A database will allow for the determination of threshold values for both healthy and diseased rotator cuff tissues. Threshold values distinctly characterizing statistically significant separation between healthy and diseased tissues can then be used to determine and mark tissues at risk.

APPENDICES

APPENDIX A

Filing Documentation for U.S. Provisional Patent Application Serial No. 61/707,312

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October 8, 2012, 2012

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Re: U.S. Provisional Patent Application Serial No. 61/707,312
Inventor: Kwartowitz et al.
Patent Application *DEVICES THAT COOPERATE WITH ULTRASOUND
PROBES FOR MUSCOSKELETAL EVALUATIONS AND RELATED SYSTEMS
AND METHODS*
Our Ref. No. 9662-56PR; Your Ref. No. 2012-106

Dear Janet:

The above-referenced application and related documents were electronically filed using the U.S. Patent and Trademark Office ("USPTO") Electronic Filing System on September 28, 2012 and has been accorded U.S. Patent Application Serial Number 61/707,312. Attached for your records is a copy of the application as filed, along with a copy of the electronic filing receipt.

Out of an abundance of caution, we are requesting that you confirm that the proper inventive entity has been identified for the claimed invention. Presently, we have **David Kwartowitz; Erika Trent; Fuad Mefleh; Vipul Pai Raikar and Delphine Dean** identified as joint inventors for this application. As you may be aware, inventorship is determined by the subject matter of the claimed invention. Generally stated, to be an inventor one must have made an actual contribution to the conception of the operative invention that is claimed. There may be joint inventorship even though the joint inventors (a) did not work physically together or at the same time, (b) did not make an equal contribution, or (c) did not make a contribution to the subject matter of every claim of the patent. A worker who merely carries out the instructions of another or only provides implementing devices to carry out another's ideas where the effort to do so is the exercise of one of ordinary skill is not typically an inventor. Further, persons listed as contributing to an article describing or related to the invention are not necessarily inventors.

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October 8, 2012
Page 2 of 2

Please feel free to call with any questions that you may have on this issue. There is no need to reply on this matter if the proper inventive entity has been named.

The report of invention stated that no government funding was used to develop the invention. Please let us know if this is incorrect. Also, we filed the application with an assertion of small entity status. Please also let us know if this is incorrect.

Also, attached for execution by the inventors is an Assignment. **Please return the executed Assignment for filing with the USPTO.**

As always, please feel free to call us with any questions that you may have.

Best regards,

Sincerely,

A handwritten signature in black ink, appearing to read "Julie H. Richardson", with a stylized flourish at the end.

Julie H. Richardson

JHR/clr
Attachments

cc: Ms. Lisa Perpall (via email)

APPENDIX B

Force Measuring Device Design Drawings

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